PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 1157WOORD01	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/EP2004/000196	International filing date *(day/month/year)* 14.01.2004	Priority date *(day/month/year)* 14.01.2003
International Patent Classification (IPC) or national classification and IPC A61K31/502, A61P35/02, A61P35/00, A61K31/00, A61K31/44		EINGANG RECEIVED 16. Feb. 2005 Gewerblicher Rechtsschutz
Applicant ALTANA PHARMA AG et al.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 10 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☒	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☒	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
14.07.2004	15.02.2005
Name and mailing address of the International preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465 PCT/IPEA/409	Authorized Officer Pacreu Largo, M Telephone No. +49 89 2399-7851

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-21 as originally filed

   Claims, Numbers

   1-85 as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. II Priority

1. ☒ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:
   - ☒ copy of the earlier application whose priority has been claimed (Rule 66.7(a)).
   - ☐ translation of the earlier application whose priority has been claimed (Rule 66.7(b)).

2. ☐ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rule 64.1). Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 50-69,79-82,85; 24,49,70 and partially 15-19,39-44,62-65,71-85; 25-49,75-78 and 84 with respect to inductrial applicability

because:

☒ the said international application, or the said claims Nos. 25-49,75-78 and 84 with respect to industrial applicability relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 50-69,79-82,85 are so unclear that no meaningful opinion could be formed *(specify)*:

see separate sheet

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 24,49,70 and partially 15-19,39-44,62-65,71-85

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation to restrict or pay additional fees, the applicant has:
   - ☐ restricted the claims.
   - ☒ paid additional fees.
   - ☐ paid additional fees under protest.
   - ☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1-14, 20-23,25-38, 45-48,50-61,66-69 and in part: 15-19,39-44,62-65,71-85 .

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-23,25-48,71-78,83-84
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-23,25-48,71-78,83-84
Industrial applicability (IA)	Yes:	Claims	1-23,71-74,83
	No:	Claims	

2. Citations and explanations (Rule 70.7):

   see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

III.1 Claims 25 to 49, 75 to 78 and 84 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

III.2 It is at present not clear in the sense of Art. 6 PCT what is the scope of claims 50-69, 79-82 and 85 reading "Treatment combination for neoplasms of lymphoid cells comprising ...". Therefore, no opinion on patentability of these claims will be performed. However, the following comments can already be made:
- if claims 50-69, 79-82 and 85 are directed to the use of the combinations claimed for the treatment of neoplasms of lymphoid cells, the arguments for novelty and inventive step given in paragraphs V.2-V.4 would apply.
- if claims 50-69, 79-82 and 85 are directed to the combinations per se (product claims), documents D14-D17 would be novelty destroying for at least some of the claims.

Re Item IV

Lack of unity of invention

IV.1 The problem to be solved by the present application is the provision of compounds for the treatment of neoplasms of lymphoid cells, specially for the treatment of leukemia.

The solution proposed is the use of various PDE4 inhibitors, namely:

Invention 1: claims 1-14, 25-38, 50-61 and 71-85 (in part)
Use of compounds of formula 1 or compounds of formula 2 for the manufacture of a medicament for the treatment of neoplasms of lymphoid cells; combinations of compounds of formula 1 or compounds of formula 2 with one or more differentiation inducing agents and/or an agent effective in raising intracellular concentrations of cAMP or a stable analog of cAMP.

Invention 2: claims 15-19 (in part), 20-23, 39-44 (in part), 45-48, 62-65 (in part), 66-69, 71-85 (in part)
Use of piclamilast, roflumilast, roflumilast-N-oxide, AWD-12-281, AWD-12-343 or SCH-351591 for the manufacture of a medicament for the treatment of neoplasms of lymphoid cells; combinations of piclamilast, roflumilast, roflumilast-N-oxide, AWD-12-281, AWD-12-343 or SCH-351591 with one or more differentiation inducing agents and/or an agent effective in raising intracellular concentrations of cAMP or a stable analog of cAMP.

Invention 3: claims 15-19 (in part), 24, 39-44 (in part), 49, 62-65 (in part), 70, 71-85 (in part)
Use of V-11294A, CDC-801 or cilomast for the manufacture of a medicament for the treatment of neoplasms of lymphoid cells; combinations of V-11294A, CDC-801 or cilomast with one or more differentiation inducing agents and/or an agent effective in raising intracellular concentrations of cAMP or a stable analog of cAMP.

Invention 4: claims 15-19, 39-44, 62-65 and 71-85 (all in part)
Use of compound CI-1018 for the manufacture of a medicament for the treatment of neoplasms of lymphoid cells; combinations of compound CI-1018 with one or more differentiation inducing agents and/or an agent effective in raising intracellular concentrations of cAMP or a stable analog of cAMP.

Invention 5: claims 15-19, 39-44, 62-65 and 71-85 (all in part)
Use of compound arofylline for the manufacture of a medicament for the treatment of neoplasms of lymphoid cells; combinations of compound arofylline with one or more differentiation inducing agents and/or an agent effective in raising intracellular concentrations of cAMP or a stable analog of cAMP.

Invention 6: claims 15-19, 39-44, 62-65 and 71-85 (all in part)
Use of compound atizoram for the manufacture of a medicament for the treatment of neoplasms of lymphoid cells; combinations of compound atizoram with one or more differentiation inducing agents and/or an agent effective in raising intracellular concentrations of cAMP or a stable analog of cAMP.

Invention 7: claims 15-19, 39-44, 62-65 and 71-85 (all in part)

Use of compound lirimilast for the manufacture of a medicament for the treatment of neoplasms of lymphoid cells; combinations of compound lirimilast with one or more differentiation inducing agents and/or an agent effective in raising intracellular concentrations of cAMP or a stable analog of cAMP.

Invention 8: claims 15-19, 39-44, 62-65 and 71-85 (all in part)
The chemical structure of compounds CDC-998, CC-1088, IC-485 and KW4490 is unknown. Therefore, it is not possible to assess if they represent separate inventions or a group of inventions.

The use of PDE4 inhibitors (alone or in combination with a differentiation inducing agent such as fludarabine or an agent that raises intracellular concentrations of cAMP such as forskolin) for the treatment of leukemia is already known in the prior art, see e.g. the following documents: Norman P., Expert Opinion on Therapeutic Patents, 2000; Lerner et al, Leukemia & Lymphoma, 2000; WO0016621; Siegmund et al, Leukemia (Basingstoke) 2001; Ogawa Ryosuke et al, Blood, 2002; Kato et al, Pedriatic Research, 2001.

Therefore, the use of PDE4 inhibitors (or combinations thereof) for the treatment of neoplasms of lymphoid cells cannot account any longer as common inventive concept linking the various items 1 to 8 above. Furthermore, the compounds of items 1 to 8 are structurally different and therefore no unifying concept can be acknowledged.

Since there is no other special technical feature that could fulfil the role of special technical feature in the sense of Rule 13 PCT, the present application lacks unity of invention, containing the subject-matters as listed.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

V.1 The documents cited in the Search Report are consecutively numbered D1-D17 in the order of their listing. If not indicated otherwise, reference is made to the passages cited in said ISR.

V.2 The use of compounds of formula 1, formula 2, roflumilast, roflumilast-N-oxide,

piclamilast, AWD-13-281, AWD-12-343 or SCH-351591 (either alone or in combination with one or more differentiation inducing agents and/or an agent effective in raising intracellular concentrations of cAMP or a stable analog of cAMP) for the preparation of a medicament for the treatment of neoplasms of lymphoid cells has not been previously disclosed in the prior art.

Thus, the subject-matter of claims 1-23, 25-48, 71-78, 83 and 84 appears to be novel, Art. 33(2) PCT.

V.3 However, the present application cannot be considered as involving an inventive step (Articles 52(1) and 56 EPC) for the following reasons:

Document D8 is directed to the use of PDE4 inhibitors for the treatment of chronic lymphocytic leukemia. Documents D7, D9 and D10 disclose studies which directly point at the use of PDE4 inhibitors in the therapy of lymphoid malignancies. Most of them refer to rolipram, which is a reference agent for PDE4 inhibitors in *in vitro* experiments (see D9, page 1568, first column, lines 29-30).

The subject-matter of the present application differs from D7, D8, D9 and D10 in that the PDE4 inhibitors of formula 1 or 2, or piclamilast, roflumilast, roflumilast-N-oxide, AWD-12-281, AWD-12-343 or SCH-351591 are used to treat neoplasms of lymphoid cells.

The problem to be solved may therefore be regarded as providing alternative PDE4 inhibitors for the treatment of the mentioned diseases.

Document D1 discloses compounds of formula 1 as effective PDE4 inhibitors.
Document D2 relates to compounds of formula 2 which are also described as being effective PDE4 inhibitors.
D3 refers to roflumilast, its N-oxide and piclamilast, which are known PDE4 inhibitors more potent than rolipram.
From D4-D6 it is also known that AWD-12-281, AWD-12-343 and SCH-351591 are selective inhibitors of PDE4.

The skilled person, willing to find alternative PDE4 inhibitors for the treatment of leukemia, would try to use known PDE4 inhibitors such as those described in D1-D6.

Therefore, claims 1, 5-7, 11-15, 19-23, 25, 29-31, 35-39, 44-48 and 83-84 cannot be considered as involving an inventive step, Art. 33(3) PCT.

V.4 D8 (see examples 3, 4 and 8), D9 (cf. abstract and page 1568, first column, lines 1-3), D10 (cf. abstract and discussion) and D11 further disclose that PDE4 inhibitors may be combined with other drugs such as forskolin, fludarabine or glucocorticosteroids. The combinations results in at least additive effects. Furthermore, document D15 also discloses the combination of PDE4 inhibitors with known antineoplastic agents for the treatment of different cancers.

In the light of these disclosures and for the same reasons as put forward in paragraph V.3, the subject-matter of claims 2-4, 8-10, 16-18,26-28, 32-34, 40-42, 71-78, 83 and 84 does not involve an inventive step, Art. 33(3) PCT.

V.5 For the assessment of the present claims 25 to 49, 75 to 78 and 84 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.